The Clinical Spectrum of Primary Lateral Sclerosis

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Abstract

Primary lateral sclerosis is a distinct entity that has recently been classified as a "restricted phenotype" of ALS. It is characterized by a pattern of isolated upper motor neuron involvement that often begins in the legs and spreads diffusely. Distinction from other conditions requires careful consideration of clinical presentation and time course of disease. Mills' Syndrome is a rare unilateral variant of primary lateral sclerosis. Cognitive and behavioral involvement may occur.

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Introduction

Primary lateral sclerosis (PLS), which is classified as a "restricted phenotype" of amyotrophic lateral sclerosis (ALS) in the most recent revision of the El Escorial Criteria,[1] is an isolated form of upper motor neuron (UMN) disease that carries a relatively benign prognosis when compared to ALS. When diagnostic criteria (to be discussed later in this supplement) are strictly applied, most ALS clinics will report that their population is comprised of about 2-3% of patients with PLS. These patients can represent a diagnostic challenge, as early in presentation, it can be difficult to distinguish between PLS and UMN-onset ALS and late-onset hereditary spastic paraplegia (HSP). Indeed, the diagnosis of PLS cannot be properly made until at least 3-4 years has passed without the development of lower motor neuron (LMN) signs. ALS and PLS share many common features, including the potential for cognitive involvement, causative or contributory genetic mutations, and pathological and neuroimaging features.

Primary Lateral Sclerosis Clinical Presentation

PLS is a slowly progressive neurodegenerative disorder affecting the upper motor neurons, typically presenting in middle age and rarely before the third decade.[2] PLS affects both sexes, with a slight male predominance. PLS occurs on a spectrum of motor neuron disorders with progressive muscular atrophy at one end (pure lower motor neuron (LMN) dysfunction), ALS in the middle (combined UMN and LMN dysfunction) and PLS at the other end.[3] The diagnosis of PLS is a diagnosis of exclusion, with a work up consisting of lab work, neuroimaging, and electromyography. Most diagnostic criteria include an element of time – by 3-4 years the chance of converting to ALS is small.[4-6] The UMN dysfunction in PLS patients presents in one of two ways.[7] The most common presentation is leg involvement, which can be unilateral or bilateral;

patients typically notice gait changes, decreased balance, or falls. Less frequently, patients present with bulbar dysfunction, manifesting as difficulty speaking or swallowing. UMN signs in the limbs include hyperreflexia, spasticity and increased tone, extensor plantar response, slowing of finger or foot tapping, and weakness in an UMN pattern (hip flexors, knee flexors and ankle dorsiflexors most affected). Bulbar UMN signs include brisk jaw jerk, facial reflexes, spastic dysarthria, dysphagia, and pseudobulbar affect (emotional lability with fits of laughter or crying). PLS can be distinguished from ALS, as there is usually not muscle wasting or fasciculations, and EMG generally is normal or only shows mild denervating changes in limited muscles.[4] The disorder is slowly progressive over years. If onset is in the legs, it generally progresses next to the arms (~3-4 years) and then to bulbar involvement (~5 years), although bulbar involvement may precede arm involvement. If onset is in the bulbar region, it then slowly progresses to the limbs, either the legs or the arms but eventually typically all regions are involved.[2, 7] PLS can be distinguished from HSP, which can have an earlier age of onset, positive family history, typically affects both legs, and often does not progress to involve multiple regions.[8] The rate of progression in PLS is much slower than in ALS, and often is not life-limiting. Various series report average symptom duration from 7 to 14 years. However, dysphagia can lead to aspiration, and advanced disease can lead to complications related to immobility. Other less frequent manifestations include urinary frequency in one third to one half of patients, and while visual symptoms are not reported, on examination eye movement abnormalities may include saccadic breakdown of smooth pursuits or supranuclear paralysis.[2] Global cognition can be impaired in a pattern similar to ALS with frontotemporal dementia (FTD).[9] There are no FDA approved treatments for PLS, and treatment usually requires a multidisciplinary approach: assessment for gait and mobility aids; treatment of spasticity with anti-spasticity drugs or trials of intrathecal baclofen; and use of dextromethorphan/quinidine combination if pseudobulbar affect is present.

Distinguishing Primary Lateral Sclerosis from Amyotrophic Lateral Sclerosis

It can be challenging to determine when a clinical presentation represents a predominantly UMN presentation/onset of ALS distinct from PLS. Although the definitions may seem straightforward, as we evaluate more and more cases, the lines blur and an argument for a continuum of disease can be made.[10] There are some features of the history, exam, laboratory findings and progression of disease that, when present, should direct the clinician to consider PLS rather than ALS.

To begin, there are several historical features that should shift attention from ALS to PLS. The presence of stiffness on presentation, especially in the lower extremities, suggests PLS. A retrospective study including review of 661 ALS and 43 PLS subjects found that stiffness was the only significantly different presenting symptom between the two groups and was present in 47% of PLS and 4% of ALS subjects.[11] Leg stiffness is the cause of early balance difficulties often seen in PLS. Additionally, the duration of symptoms is important and symptoms present for more than 3-5 years suggest a diagnosis other than ALS. In one retrospective study,[12] 34 patients (9 PLS, 15 UMN dominant ALS and 10 ALS) were compared on the basis of their presenting symptoms. PLS patients were stronger, more likely to have limb onset, and had a prolonged duration of symptoms (57.7 months) prior to first evaluation.

On exam, evidence of LMN findings including atrophy and fasciculations in the context of hyperreflexia or other UMN findings makes a diagnosis of ALS more straightforward. Conversely, ALS can present with only UMN findings.[11] Additionally, patients with PLS may demonstrate atrophy, though the statistics on this vary widely with numbers reported between 2%[11] and 22%.[12] Additionally, focal weakness and bulbar involvement make ALS more likely.[11] The presence of cognitive involvement suggests ALS, but up to 3.3% of PLS patients can have frontotemporal dementia. Similarly, genetic mutations that are typically thought

to be associated with ALS may be found in patients with a phenotype suggesting PLS, as the C9orf72 expansion has been reported in this cohort.[13]

Evaluation for motor neuron disease includes imaging and additional testing to exclude other causes for the syndrome. Electrodiagnostic studies remain an integral part of the assessment. A normal EMG that includes muscles from the bulbar, cervical, thoracic and lumbosacral segments should bring the diagnosis of ALS into question, although early in disease, the EMG can be benign. It should be noted, though, that up to 45% of PLS patients followed over time had mild electrodiagnostic changes of denervation.[4] Central nervous system motor conduction studies that demonstrate cortical inexcitability rather than hyperexcitability by transcranial magnetic stimulation would support a diagnosis of ALS rather than PLS, although these studies are not part of the usual clinical evaluation.

Rate of disease progression is a key factor in differentiating ALS from PLS. Slow progression over time without atrophy or wasting would mitigate against the diagnosis of ALS. In one large cohort, disease duration was significantly longer in PLS compared to ALS (11.2 +/- 6.1 vs 3.8 +/- 4.2 years) and over 16 years of follow-up, the mortality rate was significantly lower in patients with PLS compared with patients with ALS (only 33% vs 89%, respectively; P<.001).[11] Additionally, wasting was observed in 100% of ALS subjects but only 2% of PLS subjects[11] suggesting that ALS should not be considered when there is no wasting observed over time. These authors suggested that a person presenting with spasticity who does not develop wasting within 3 years most likely has PLS and not ALS[11] while others[12] have used 4 years as the defining time point for distinction. Other features that suggest a diagnosis other than ALS include a lack of weight loss, preserved vital capacity and preserved strength over time.[11]

Distinguishing Primary Lateral Sclerosis from Hereditary Spastic Paraplegia

HSP and PLS are heterogeneous, at times overlapping clinical syndromes that share UMN-related motor disturbance.[6, 14, 15] HSP and PLS syndromes are diagnosed by their symptoms, course, neurologic findings and by the exclusion of alternate disorders; rather than by "positive findings" on neuroimaging, electrodiagnostic studies, neuropathology, or laboratory (including genetic) tests. HSP and PLS differ by the distribution of UMN-related motor impairment, which occurs primarily in the legs in HSP and usually is more widespread in PLS, and by the frequent occurrence of additional neurologic impairments in many forms of HSP that do not occur in PLS (**Table 1**).

Symptom-onset and course in HSP can be either as an early childhood onset, nonprogressive, spastic paraparesis (resembling spastic diplegic cerebral palsy) or as a later-onset, insidiously progressive spastic gait, with or without additional neurologic impairment. Although there are many childhood-onset, non-progressive forms of HSP, there are no childhood-onset, non-progressive forms of PLS. PLS, whether beginning in childhood or adulthood, progresses slowly over years.

In "uncomplicated" HSP, UMN-related motor disturbance exclusively involves the legs. Of note, asymptomatic upper extremity hyperreflexia without weakness, spasticity, or impaired dexterity is common in HSP. The UMN-related motor disturbance of many forms of "complicated" HSP involves upper extremity and bulbar muscles in addition to the legs. Therefore, in complicated HSP, the distribution of UMN-related motor impairment is similar to that of PLS.

"Uncomplicated" HSP is a motor-sensory disorder primarily affecting the corticospinal tracts with mild involvement of the dorsal columns. At least half of the >100 forms of HSP are associated with additional neurologic abnormalities

including, but not limited to, peripheral neuropathy, ataxia, dementia, intellectual disability, seizures, cataracts, optic atrophy, and muscle atrophy.

For many patients with PLS, this is not exclusively an UMN disorder. In addition to UMN disturbance, additional neurologic involvement in PLS is limited to frequent pseudobulbar affect and urinary urgency, variable cognitive impairment, and occasional subtle dorsal column impairment.[16] Beyond this, the other neurologic abnormalities that frequently accompany many forms of HSP are not features of PLS. Muscle atrophy (usually distal, symmetric, and insidiously progressive) occurs in a number of forms of complicated HSP. Although electromyographic evidence of minimal LMN disturbance may occur late in the disorder, marked muscle atrophy is not a feature of PLS.[11, 12]

HSP diagnosis does not require the occurrence of similarly affected family members or identification of a causative gene mutation. Family history of similar disorder is often absent in HSP patients (e.g. due to *de novo* gene mutations or because of X-linked or autosomal recessive inheritance). Genetic testing, including whole exome sequencing, does not identify a causative gene mutation in approximately 40-50% of HSP patients. While finding a pathogenic mutation in an HSP-associated gene confirms and adds molecular precision to the clinical diagnosis, the absence of an identified mutation does not refute the diagnosis of HSP. Although the majority of PLS patients have no family history of similar disorder, both autosomal recessive[17] and dominant[18] forms of PLS have been described. Therefore, occurrence of similarly affected first-degree relatives, though rare, does not exclude a diagnosis of PLS. The vast majority of patients with PLS have no identified gene mutation. Occasionally, pathogenic gene variations are identified in genes implicated in ALS (e.g. ALS2, FIG4, C9orf72) and HSP (SPG7/paraplegin). Finding a pathogenic mutation (e.g. in SPG7 or C9orf72) in a PLS patient does not change the diagnosis (e.g. to SPG7 HSP or FTD-ALS, respectively). Rather, such discoveries extend knowledge of the various manifestations of these gene variations.

HSP and PLS are overlapping clinical syndromes that share UMN-related motor impairment. Distinction between these conditions relies on the distribution of UMN-related functional impairment; and the occurrence of additional neurologic abnormalities that are common in many types of HSP but which do not occur in PLS.

Mills' Syndrome – A Rare Form of a Rare Disease

American neurologist Charles Karsner Mills (1845-1931) presented a case of "unilateral progressive ascending paralysis" to the Philadelphia Neurological Society in 1899.[19] It concerned a 52-year-old male with a two-year history of slowly-progressive right leg, followed by right arm weakness, associated with UMN signs and no significant sensory loss, but lacking muscle atrophy to suggest ALS. Mills' syndrome has become a clinical phenotype often considered as 'unilateral PLS'.

Gastaut and Bartolomei reviewed Mills' eight cases, five others published between 1927 and 1951, and two of their own.[20] They identified the core features of a slowly-ascending hemiparesis over months to years (13/15 cases), often with bilateral pyramidal signs (7/15). There was no electromyographic evidence of LMN involvement in repeated assessments of their own cases, both of whom survived into a second decade from symptom onset. A degree of facial weakness was sometimes noted (5/15) and occasional minimal hyperaesthesia (3/15, including Mills' original case).

Alongside University of Pennsylvania colleague William Gibson Spiller (1863-1940), Mills described another case of his syndrome, involving progressive right hemiplegia, with *post mortem* histopathological analysis.[21] Travelling upwards from the medulla, they noted: "intense and long-standing degeneration of the right crossed and the left direct pyramidal tracts…extending into the pons but not into the left cerebral peduncle…(with) comparatively recent degeneration of the

left crossed and right direct pyramidal tracts, traced…into the lower part of the right internal capsule. No lesions, degenerative or focal, were found elsewhere in the brain or spinal cord...” Sections of the left paracentral lobule were reported to contain normal-appearing Betz cells, so that their overall conclusion was a “primary pyramidal tract degeneration” rather than occurring secondary to a cortical hemispheric lesion.

A case of Mills’ syndrome underwent positron emission tomography using [11C]-PK11195, demonstrating unilateral microglial activation in the region of the motor cortex contralateral to the ascending hemiparesis as well as in the descending corticospinal tracts.[22] Against this cortical microglial activation representing a more caudal dying back phenomenon, a *post mortem* case of progressive unilateral hemiplegia was shown to have significant additional microglial infiltration of the uncrossed corticospinal tract in the cervical cord. This implies a degenerative process defined according to ‘top-down’ anatomy, although that case was atypically rapidly-progressive and associated with aphasia.[23] (**Figure 1**)

Mills himself acknowledged multiple potential aetiologies for his syndrome of ascending (and more rarely also descending) progressive hemiplegia, beyond a primary neurodegenerative hypothesis. These included “disseminated sclerosis”, a unilateral form of ALS, unilateral “paralysis agitans”, focal cerebral or spinal lesions, a manifestation of neurosyphilis, and functional.[24] With the development of magnetic resonance imaging sensitive to white matter pathology, Mills’ syndromes due to “solitary sclerosis” are more recognized.[25, 26] With the technological developments in mind, Maragakis and colleagues reviewed five locally-acquired cases with Mills’ phenotype.[27] All five were said to meet Pringle criteria for PLS,[6] but all with atypical asymmetry of limb weakness. There was a notably wide-ranging age at symptom onset (41-86 years).

A thorough consideration of secondary causes for the syndrome of progressive hemiplegia is mandatory, but rare cases of ‘essential’ (idiopathic) Mills’ syndrome

will continue to emerge. They should, like PLS, be supported in terms of care under the broader diagnostic umbrella of neurodegenerative disorders of the motor system.

Cognitive and Behavioral Symptoms in PLS

The discovery of the phenotypic overlap between ALS and FTD has prompted the question: What is the relationship, if any, between PLS and the cognitive and behavioral symptoms associated with FTD? Approximately 15% of ALS patients meet criteria for FTD, with up to 50% of ALS patients demonstrating at least some cognitive or behavioral symptoms.[28-30] In the latest version of the El Escorial criteria, PLS is defined as a restricted motor phenotype associated solely with neurodegeneration in the motor cortex.[31] Thus, according to this definition, PLS is a priori not associated with degeneration of non-motor association frontal cortex. However, since the 1990s neuropsychological examination of PLS patients have revealed frontotemporal cognitive abnormality.[32] A review of all reports of changes in cognition and/or behavioral changes observed in PLS found 33 publications reporting on 307 patients. Seven (2.3%) had frank FTD and 68 had changes in cognition or behavior that did not meet criteria for FTD.[13] A subsequent study reported 49% of PLS patients showing some degree of cognitive and/or behavioral abnormality.[28] In general, the symptoms reported in these publications are consistent with the cognitive and behavioral symptoms associated with FTD, rather than those of other types of dementia such as Alzheimer's disease. A retrospective meta-analysis of 33 publications[13] found that executive dysfunction was the most commonly observed impairment in PLS samples, yet language deficits and memory impairment were also seen. And notably, mutations associated with FTD, including hexanucleotide repeat expansions in C9orf72, have been detected in patients with PLS.[33, 34]

Due to the relative rarity of PLS, it is difficult to draw definitive conclusions from the reported prevalence of non-motor symptoms in PLS, but the data reported

suggest that cognitive and/or behavioral symptoms associated with involvement of non-motor frontal cortex occurs in a subset of PLS patients, while the exact relative prevalence of non-motor symptoms in PLS compared with ALS is debatable. But the prevalence of these non-motor symptoms appears to be not grossly dissimilar in PLS (22-49%) compared with ALS (up to 50%). A retrospective study of 277 ALS patients and 75 PLS patients[28] found that high frequencies of cognitive and behavioral abnormalities were seen in both groups. They had similar rates of impairment, which were dysexecutive in nature. In the sample, the PLS group was distinguished by having the highest impairment on the FTD-Q behavioral scale. Comprehensive neuropsychological examination of frontal lobe function in a sample of 20 PLS patients[35] revealed impairment in executive functioning, free recall and delayed memory. The impairment was mild to moderate in nature and it varied by person. A portion of the patients displayed clinically significant deficits that did not reach the dementia threshold. In a study directly comparing cognitive and behavioral features of patients with ALS and PLS, both the pattern and rate of impairment was equivalent across the groups. Both groups had considerable heterogeneity, yet both demonstrated cognitive impairment (39% of the PLS group and 31% of the ALS group). The impairment was predominantly dysexecutive in nature. It was notable that the majority of the PLS patients had measurable behavioral impairment.[36] A pattern of PLS patients having higher rates of behavioral impairment than their ALS counterparts[28, 36] was substantiated in a PLS sample studied as part of a prospective multicenter study of ALS.[37] In this sample, 37 PLS subjects completed cognitive and behavioral tests described elsewhere. The rate of patients meeting criteria for FTD and impairment on the behavioral and cognitive subscales were higher in the PLS than ALS groups.

Imaging studies show correlation between cognitive deficits and extra-motor cortex biomarkers. A diffusion tensor MRI study of PLS patients revealed that 10 of the 21 patients examined had cognitive abnormalities on neuropsychological exam. Of the cognitively abnormal subset, diffusion tensor MRI abnormalities confirmed significant white matter tract abnormalities on all three parameters (fractional anisotropy, radial diffusivity and mean diffusivity).[38] Cerebral hemodynamic changes were observed among cognitively impaired PLS patients, with reduced cerebral blood flow with increased mean transit time in all brain regions, with predominant deficits in the frontotemporal regions.[39] In a transcranial magnetic stimulation (TMS) study of PLS patients that also included neuropsychological exam, the PLS sample of 21 displayed globally impaired cognition paired with significantly higher resting motor threshold on TMS, which is consistent with corticospinal axon deterioration.[9]

These findings have several practical implications. The current criteria for PLS specify involvement of only motor cortex, but involvement of non-motor cortex appears to occur in many cases of PLS. These findings suggest that all PLS patients should be screened for non-motor symptoms, and that these symptoms should be addressed when present. Finally, patients with PLS should be considered for therapeutic trials targeting non-motor symptoms and/or non-motor regions of the frontal cortex. Future studies of PLS patients will benefit from employing sensitive measures of frontotemporal cognitive change, including an instrument to measure FTD-type behavior change. It is possible that because PLS patients maintain a longer lifespan than their ALS counterparts, their behavior changes may have more time to evolve.

Conclusion

PLS is a distinct entity with a definable clinical presentation and course. The most recent version of the El Escorial Criteria deems it a “restricted phenotype” of ALS. PLS is most commonly characterized by isolated UMN signs with onset

in the legs and slow progression to eventual diffuse motor involvement. Clinically it is important to distinguish between PLS and UMN-onset ALS and between PLS and HSP. Extramotor features most commonly include pseudobulbar affect and bladder urgency; cognitive involvement resembles that seen in frontotemporal dementia with a prominent dysexecutive component. Future directions include developing technologies to better define the UMN pathology in PLS, including transcranial magnetic stimulation and neuroimaging modalities, streamlining the diagnostic criteria, and validating the tools to measure change in order to support clinical trials.

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